REMARKS

Formal Matters

Claims 1-3 and 20-22 are pending.

Claims 1-3 and 20-22 were examined and rejected.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Specification

The instant specification has been objected to for containing embedded hyperlinks.

The specification has been amended to remove embedded hyperlinks.

Withdrawal of this rejection is respectfully requested.

Rejections under 35 U.S.C. § 103- general discussion

All of the pending claims are rejected as obvious over Bryan (who discloses a wild-type *Renilla* GFP sequence), in combination with one or more secondary references that allegedly fill the void between Bryan's disclosure and what is being claimed. Although each rejection is different, the general thrust of each rejection is the same: Bryan's wild-type *Renilla* GFP, in combination with the retroviral vector of a secondary reference, renders the instant claims obvious. The Examiner argues that one of skill in the art would be motivated to make and use the claimed subject matter because the spectral properties of wild-type *Renilla* GFP were well known to be superior to the spectral properties of wild-type *Aequoria* GFP - the "industry standard" GFP in the mid to late 1990's.

The Applicants agree with the Examiner in that the amino acid sequence of wild-type *Renilla* GFP was known prior to filing of their patent application. The Applicants also agree that retroviral vectors containing altered *Aequoria* GFP were well known and had been successfully used prior to filing their patent application. Finally, the Applicants agree that the superior spectral properties of wild-type *Renilla* GFP were well known prior to filing their patent application. Notwithstanding these facts, the Applicants believe that the claimed vector is patentable over the cited art because the art at the time of filing indicates a lack of a reasonable expectation of success in using the claimed vector.

In *Graham v. John Deere* (1966), the Supreme Court held that in making a determination of obviousness under 35 U.S.C. § 103 the courts and the Patent and Trademark Office should make several basic factual inquiries. One of the required inquiries is "the scope and content of the prior art".[1]

Further, the case law is replete with decisions that recognize that an invention that otherwise might be viewed as an obvious modification of something known in the prior art will not be deemed obvious in a patent law sense because of uncertainty in the art or the absence of a reasonable probability of success.[2] In other decisions, nonobviousness and patentability are found when one or more prior art references "teach away" from the invention.[3] Disclosures that diverge from and teach away from the invention cannot be disregarded.[4]

In particular, the Supreme Court stated in *United State v. Adams* that "known disadvantages in old devices which would naturally discourage the search for new inventions may be taken into account

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[1] *Graham v. John Deere*, 383 U.S. 1, 17, 148 USPQ 459 (1966).

[2] E.g. *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1354, 65 USPQ2d 1961 (Fed. Cir. 2003) ("there can be little better evidence negating an expectation of success than actual reports of failure. See, e.g., In re Rinehart, 531 F.2d 1048, 1053-54, 189 USPQ 143, 148-49 (CCPA 1976).)"); *Ortho Pharmaceutical Corp. v. Smith*, 959 F.2d 936, 943, 22 USPQ2d 1119, 1125 (Fed. Cir. 1992); *Hybritech Inc. v. Monoclonal Antibodies, Inc.* 802 F.2d 1367, 231 USPQ 81 (Fed. Cir. 1986); *Merck & Co. v. Danbury Pharmacal Inc.*, 694 F. Supp. 1, 29, 8 USPQ2d 1793, 1816 (D. Del. 1988), aff'd, 873 F.2d 1418, 10 USPQ2d 1682 (Fed. Cir. 1989).

[3] E.g *Gillette Co. v. S.C. Johnson & Sons, Inc.*, 919 F.2d 720, 724, 16 USPQ2d 1923, 1927 (Fed. Cir. 1990) (the closest prior art reference "would likely discourage the art worker from attempting the substitution suggested by [the inventor/patentee]."). See also *Singh v. Brake*, 317 F.3d 1334, 1346, 65 USPQ2d 1641 (Fed. Cir. 2003) ("whether or not a reference 'teaches away' from a claimed invention" is "relevant in determining whether or not a claimed invention would have been obvious"); *In re Peterson*, 315 F.3d 1325, 1331, 65 USPQ2d 1379 (Fed. Cir. 2003) ("an applicant may rebut a prima facie case of obviousness by showing that the prior art teaches away from the claimed invention in any material respect."); *McGinley v. Franklin Sports, Inc.*, 262 F.3d 1339, 1354, 60 USPQ2d 1001 (Fed. Cir. 2001) If references taken in combination would produce a 'seemingly inoperative device,' we have held that such references teach away from the combination and thus cannot serve as predicates for a prima facie case of obviousness. *In re Sponnoble*, 405 F.2d 578, 587, 160 USPQ 237, 244, 56 C.C.P.A. 823 (1969) (references teach away from combination if combination produces "seemingly inoperative device"); see also *In re Gordon*, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984) (inoperable modification teaches away)."); *In re Haruna*, 249 F.3d 1327, 1335, 58 USQP2d 1517 (Fed. Cir. 2001) ("A reference may be said to teach away when a person of ordinary skill, upon reading the reference, ... would be led in a direction divergent from the path that was taken by the applicant.' *Tec Air, Inc. v. Denso Mfg. Mich. Inc.*, 192 F.3d 1353, 1360, 52 USPQ2d 1294, 1298 (Fed. Cir. 1999)."); *Mentor H/S, Inc. v. Medical Device Alliance, Inc.*, 244 F.3d 1365, 58 USPQ2d 1321, 1328 (Fed. Cir. 2001).

[4] *Dow Chemical Co. v. United States*, 20 Cl. Ct. 623, 630, 18 USPQ2d 1657, 1662 (Cl. Ct. 1990).

in determining obviousness"[5]. Likewise in *In re Sponnoble* the court stated that if a combination of references would produce a "seemingly inoperative device,"[6] then they should not be combined.

The facts surrounding this case are relatively straightforward and should logically lead to the conclusion that, at the time of filing, there would have been no reasonable expectation that the claimed retroviral vector would work. In view of this conclusion and applying current law, the claimed retroviral vectors should be patentable.

Aran, Hanazono, Levy, Cheng and Anderson[7] (the "supporting references"), which were well known and available at the time of filing, unequivocally state that retroviral vectors encoding wild-type GFPs don't work. For example Aran states that wild type GFP fluorescence was "undetectable"[8], Hanzano states that their attempts to isolating wild-type GFP-expressing lines "failed"[9], Levy stated that "wildtype GFP could never be visualized"[10], Cheng said the wild type GFP expression "failed"[11] and Andersen stated that fluorescence was "not sufficient to resolve infected from uninfected cells"[12]. These

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[5] *United States v. Adams* 383 U.S. 39, 52, 148 USPQ 479, 484 (1966)

[6] *In re Sponnoble* 405 F.2d 578, 587, 160 USPQ 237, 244, 56 C.C.P.A. 823 (1969)

[7] All references are of record. Aran, Hanzano, Levy and Chang have been discussed in great detail in prior responses. Aran and Anderson are cited in rejections under 35 U.S.C. § 103 in this response.

[8] See the first full paragraph of page 204 of Aran's disclosure, where Aran states that when a retroviral vector encoding a wild type *Aequorea* GFP was introduced into in a mammalian cell, fluorescence was "***undetectable***".

[9] Hanazono (Hum. Gene Ther. 1997, 8:1313-9) who stated in the abstract that "many attempts by our laboratory to isolate stable retroviral producer cell clones secreting biologically active vectors containing either the highly fluorescent S65T-GFP mutant or humanized GFP have ***failed***", and with reference to retroviral vectors encoding GFP, stated in the overview "***stable clones produced neither virus nor GFP***" and "GFP may not be a suitable selective marker in mammalian gene transfer systems".

[10] Levy et al. (Nature Biotechnology 1996, 14: 610-4, at p. 613, first full paragraph) who states that "Our experiments are in agreement with these results in that transient transfection which transfers multiple transgene copies of wildtype GFP expression cassettes were visualized, but we found that stable transduced lines with a single transgene copy of ***wildtype GFP could never be visualized*** by fluorescence microscopy (Table 1)".

[11] Cheng et al (Nature Biotechnology 1996, 14: 606-609) who states in the second paragraph of the introduction "the expression and detection of wildtype GFP (wtGFP) in mammalian cells reportedly ***failed***".

[12] Anderson et al (Proc. Natl. Acad. Sci. 1996 93: 8505-8511; of record and cited in this Office Action) states in the background that suboptimal excitation spectra of wild type GFP "*precludes the detection of wtGFP* when a single copy of the

statements are unequivocal, and represent fair evidence that the prospects of a retroviral vector encoding other wild-type GFPs would be quite gloomy.

Further, the landmark publications of Levy and Cheng show that successful expression of GFP using a retroviral vector *requires* altering the amino acid sequence of the GFP. As such, these references further *teach away* from what is being claimed.

The references at least show that at the time of filing there would be no reasonable expectation that the claimed retroviral vector would work. Using the language of the court in *In re Sponnoble*, *supra*, the combination of references proposed in this Office Action would produce a retroviral vector that would be "seemingly inoperative". Further, since the references teach that only non-wild type GFP can be expressed using a retroviral vector, the references teach away from what is being claimed.

Applying current case law to this fact pattern, the claimed retroviral vectors should be patentable.

In the Office Action, the Examiner attempts to undermine the Applicants' position by arguing that the Applicants' "reasonable expectation of success" arguments are directed to the *use* of the claimed vector, rather than the *making* of the claimed vector.

In response, the Applicants submit that the caselaw is very clear that evaluating the expected *operability* of the device produced by the suggested combination of references is a critical to determining non-obviousness[13]. In other words, the Examiner may argue that any molecular biologist would have a reasonable expectation of success in making the claimed vector. The question here, however, is not whether one of skill in the art could *make* the claimed vector with a reasonable expectation of success. Rather the question is whether one of skill in the art would *use* the claimed

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gene is stably integrated", and in the first paragraph of the results section, with reference to a population of cells infected with a retroviral vector encoding wild type *Aequoria* GFP, states: "the difference in *fluorescence was not sufficient* to resolve infected from uninfected cells".

[13] *McGinley v. Franklin Sports, Inc.*, 262 F.3d 1339, 1354, 60 USPQ2d 1001 (Fed. Cir. 2001) If references taken in combination would produce a 'seemingly inoperative device,' we have held that such references teach away from the combination and thus cannot serve as predicates for a prima facie case of obviousness. *In re Sponnoble*, 405 F.2d 578, 587, 160 USPQ 237, 244, 56 C.C.P.A. 823 (1969) (references teach away from combination if combination produces seemingly inoperative device); see also *In re Gordon*, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984) (inoperable modification teaches away).

vector with a reasonable expectation of success. If there is no reasonable expectation of success to use the claimed vector, then there would be no motivation to make the vector in the first place.

Since one of skill in the art would not be able to *use* the claimed vector with a reasonable expectation of success, the Applicants prior arguments still stand with equal force.

In the Office Action, the Examiner further attempts to undermine the Applicants' position by arguing that the statements made in the references that support the Applicant's position (i.e., the "supporting references") are irrelevant because they are directed to only wild-type *Aequoria* GFP and not wild-type *Renilla* GFP.

The Applicants acknowledge that *Renilla* GFP is not explicitly mentioned in any of the supporting references. In response to the Examiner's assertion, however, it would be readily apparent that one of skill in the art, in evaluating their chances of success in expressing a wild-type *Renilla* GFP using a retroviral vector, would logically look towards the closest prior art for guidance, rather than ignore the closest prior art. Since there is adequate evidence that wild type *Aequoria* GFP cannot be expressed using a retroviral vector, one of skill in the art would believe the same would very likely be true for a wild type *Renilla* GFP.

If the Examiner deems that references directed to retroviral vectors encoding *Aequoria* GFP are simply not relevant to claims directed to a retroviral vector encoding *Renilla* GFP, then such references should not be citable to render obvious claims directed to that very same subject matter.

Giving full weight to references relating to *Aequoria* GFP to support a rejection of claims directed to a *Renilla* GFP, while, at the same time, ignoring the teachings of those references to undermine the Applicants' position seems inconsistent to the Applicants. Either the teachings of these references should be given full weight in supporting the Applicants' arguments, or the rejection should be withdrawn as being based on references that are not relevant to the claimed subject matter. Either way, the rejections should be withdrawn.

The Examiner seems to be suggesting that because the supporting references do not explicitly state "don't express *Renilla* GFP using a retroviral vector – it won't work", the teachings of the supporting references are not relevant. The Applicants submit, however, that the teachings of those references show that retroviral vectors encoding wild-type GFPs is at best highly unpredictable and

more likely impossible. The teachings of those references are relevant the patentability of the rejected claims and, as such, should not be ignored.

In summary, the Applicants submit that the disclosures of Aran, Hanazono, Levy, Cheng and Anderson represent fair evidence that one of skill in the art would have no reasonable expectation of success in expressing a wild-type *Renilla* GFP using a retroviral vector. As such, the claimed retroviral vectors should be patentable, and this rejection should be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph

Claim 22, is rejected under 35 U.S.C. § 112, first paragraph, as allegedly reciting subject matter that is broader than as described in the specification as originally filed. This is a new matter rejection.

The Examiner argues that "test agents" are not recited in the application as filed.

The Examiner is directed towards the disclosure on page 40, line 22 to page 44, line 26 of the instant specification, where test agents are discussed in great detail.

The MPEP states that the subject matter of the claim need not be described literally (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement.[14] A such, the Applicants submit that this claim is fully supported by the instant specification, and this rejection may be withdrawn.

Rejection under 35 U.S.C. § 103 - Bryan and Aran

Claims 1-3 and 20 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over Bryan and Aran. The Office Asserts that Bryan's GFP, in combination with Aran's retroviral vectors, renders the subject matter of the instant claims obvious.

In view of the generally discussion set forth above, the Applicants submit that this rejection has been adequately addressed. Withdrawal of this rejection is respectfully requested.

The Applicants note that the first full paragraph of page 204 of Aran's disclosure states that when a retroviral vector encoding a wild type *Aequoria* GFP was introduced into in a mammalian cell,

[14] See MPEP § 2163.02

fluorescence was "***undetectable***". As such, Aran's disclosure, itself, teaches that the combination of Bryan and Aran would produce "a seemingly inoperative" vector.[13]

Rejection under 35 U.S.C. § 103 - Aran, Bryan and Zolutukhin

Claim 20 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Aran, Bryan and Zolutukhin. The Office Asserts that Aran's retroviral vectors, Bryan's Renilla GFP and Zolutukhin's human codon optimized GFP renders the subject matter of the instant claims obvious.

In view of the generally discussion set forth above, the Applicants submit that this rejection has been adequately addressed. Withdrawal of this rejection is respectfully requested.

The Applicants note that the first full paragraph of page 204 of Aran's disclosure states that when a retroviral vector encoding a wild type *Aequoria* GFP was introduced into in a mammalian cell, fluorescence was "***undetectable***". As such, Aran's disclosure, itself, teaches that the combination of Bryan, Aran and Zolutukhin would produce "a seemingly inoperative" vector.[13]

Rejection under 35 U.S.C. § 103 - Zolutukhin and Bryan

Claims 1-3 and 20 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Zolutukhin and Bryan. The Office Asserts that Zolutukhin's human codon optimized GFP retroviral vector, in combination with Bryan's *Renilla* GFP, renders the subject matter of the instant claims obvious.

In view of the general discussion set forth above, the Applicants submit that this rejection has been adequately addressed. Withdrawal of this rejection is respectfully requested.

Rejection under 35 U.S.C. § 103 - Bierhuizen and Bryan

Claims 1-3 and 20-22 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bierhuizen (Biochem. Biophys. Res. Comm. 1997 234: 371-375) in view of Bryan.

The Office Asserts that Bierhuizen's retroviral vectors, in combination with Bryan's GFP, renders the subject matter of the instant claims obvious.

In view of the general discussion set forth above, the Applicants submit that there would no reasonable expectation of success in using the claimed subject matter at the time of filing of the instant application. As such, this rejection may be withdrawn.

The Examiner may argue that this references describes the successful use of a retroviral vector encoding a wild type *Aequoria* GFP. The Applicants submit, however, that Bierhuizen does not undermine the Applicants' arguments because: a) Bierhousen is a single reference in a field in which many others report repeated failure; and b) Bierhousen, in fact, reports only marginal results their vector.

First, Bierhuizen notes that at 24 hours after transduction, wild type GFP expression is extremely weak compared to cells expressing mutant GFP. Further, according to the first col. of page 373, Bierhuizen's assays were performed on cells that had been transduced and then cultured for only *24 hours*. As such, Bierhuizen fails to report stable cell lines that express wild type *Aequoria* GFP. Given the teachings of Aran, Hanzano, Levy, Cheng and Anderson (cited above), such cell lines would be impossible to make. Bierhuizen's results therefore highlight the uncertainty in this field, and do not diminish the Applicants arguments.

Since Bierhuizen fails to report cells that stably express wild-type *Aequoria GFP* using a retroviral vector and also reports only very weak expression a short time after transduction, Bierhuizen's disclosure supports the Applicants' position that one of skill in the art would not practice the invention with a reasonable expectation of success.

Rejection under 35 U.S.C. § 103 – Bierhuizen in view of Bryan and Aran

Claims 1-3 and 20-22 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bierhuizen in view of Bryan and Aran.

The Office Asserts that Bierhuizen's retroviral vectors, in combination with Bryan's GFP and Aran's IRES renders the subject matter of the instant claims obvious.

In view of the generally discussion set forth above, the Applicants submit that there would no reasonable expectation of success in using the claimed subject matter at the time of filing of the instant application. As such, this rejection may be withdrawn.

The Applicants note that the first full paragraph of page 204 of Aran's disclosure states that when a retroviral vector encoding a wild type *Aequoria* GFP was introduced into in a mammalian cell, fluorescence was "***undetectable***". As such, Aran's disclosure, itself, teaches that the combination of Bryan and Aran would produce a seemingly inoperative vector.

The Examiner may argue that Bierhuizen describes the successful use of a retroviral vector encoding a wild type *Aequoria* GFP. As submitted above, however, Bierhuizen does not undermine the

Applicants' arguments because: a) Bierhousen is a single reference in a field in which many others report repeated failure; and b) Bierhousen, in fact, reports only marginal results their vector.

The Applicants arguments therefore still stand with equal force.

Rejection under 35 U.S.C. § 103 – Anderson in view of Bryan

Claims 1-3 and 20-22 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Anderson in view of Bryan.

The Office Asserts that Anderson's retroviral vectors, in combination with Bryan's GFP, renders the subject matter of the instant claims obvious.

In view of the generally discussion set forth above, the Applicants submit that there would no reasonable expectation of success in using the claimed subject matter at the time of filing of the instant application. As such, this rejection may be withdrawn.

The Applicants particularly note that Anderson states in the background section that suboptimal excitation spectra of wild type GFP "*precludes the detection of wtGFP* when a single copy of the gene is stably integrated", and in the first paragraph of the results section, with reference to a population of cells infected with a retroviral vector encoding wild type *Aequoria* GFP, states: "the difference in *fluorescence was not sufficient* to resolve infected from uninfected cells"

As such, Anderson's disclosure, itself, teaches that the combination of Anderson and Bryan would produce a seemingly inoperative vector.

CONCLUSION

The Applicants submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number RIGL-011.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: 7/24/06

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